ORIGINAL ARTICLE

A new modality for the estimation of corrected flow time via electrocardiography as an alternative to Doppler ultrasonography

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Background: Evaluation of corrected flow time (FTc) via ultrasonography is one of the suggested modalities for the assessment of intravascular volume status. This study aimed to compare the results of FTc of carotid artery measured via ultrasonography, as a measure of mechanical outcome of the cardiac cycle, with the results of FTc estimation from a new modified formula via electrocardiography (ECG), as a measure of electrical function of the cardiac cycle.

Methods: Healthy volunteers were evaluated before and after a passive leg raising (PLR) maneuver. FTc was measured concurrently before and after PLR via a modified method from ECG and via ultrasonography of the carotid artery.

Results: A total number of 98 healthy volunteers (51 women and 47 men) with a mean age of 30.69 ± 6.28 years were included. There was a significant correlation between FTc measured by ultrasonography and estimated by ECG both before PLR and after PLR ($r = .878$, $p < .0001$ and $r = .797$, $p < .0001$, respectively). Changes in FTc were slightly higher in measurements by ultrasonography compared to estimations by ECG ($22.33 \pm 17.15 \text{ ms}^{0.5}$ vs. $15.86 \pm 14.25 \text{ ms}^{0.5}$, $p = .001$).

Conclusion: Estimation of FTc via ECG is potentially an effective and feasible method for the assessment of volume status at the clinical settings. Further investigations should determine the significance of differences that may be observed between ultrasonography and ECG in patients with either dehydration or volume overload and in the need of real-time volume status assessment.

KEYWORDS

carotid artery, common, Doppler, electrocardiography, emergency medicine, intensive care units, ultrasonography

1 | INTRODUCTION

1.1 | Background

Accurate estimation of intravascular volume status is pivotal in the resuscitation of critically ill patients, particularly at emergency departments and intensive care units (Blehar, Glazier, & Gaspari, 2014).

Although intensive fluid therapy in patients with life-threatening volume depletion can prevent death and end-organ damage, volume overload is known to result in increased mortality, morbidity, and duration of hospital stay (Mackenzie et al., 2015). Unfortunately, physical examination provides only general hints to help physicians in estimating volume status. These measures including heart rate (HR) and blood pressure (BP) are not accurate or sensitive enough for prediction of

volume status and assessment of patient's response to the treatment (Saugel et al., 2011).

Pulmonary artery catheterization has been widely used for the measurement of central venous pressure (CVP), as a measure of volume status. In addition to the invasive nature of this procedure, significant rates of failure even by experienced physicians, and serious complications including arrhythmia, sepsis, and pneumothorax (Bowdle, 2014), there is little if any evidence in support of the validity and reliability of this method. In fact, Marik, Baram, and Vahid (2008) and Marik and Cavallazzi, (2013) who performed two meta-analysis, published in 2008 and 2013, suggested that CVP is no more accurate than coin flipping in the prediction of volume status and patient's response to fluid therapy (Marik et al).

1.2 | Importance

Point-of-care ultrasonography has become a common diagnostic choice, especially in the emergency department. This method is noninvasive, easy to learn, and provides real-time assessment at the patient's bedside (Evans et al., 2014). Various ultrasound modalities have been developed to provide accurate and minimally invasive assessment of volume status. In this regard, one of the most promising methods is the evaluation of the blood flow velocity waveform in the descending thoracic aorta via a nonimaging esophageal Doppler probe. This modality is based on calculating the systolic flow time with cycle time correction (corrected flow time, FTc). FTc is known to be directly associated with volume status (Dark & Singer, 2004). Although the assessment of FTc via esophageal Doppler probe limits this modality to intubated or highly sedated patients, the results of several recent studies have suggested the applicability of FTc measurement in carotid artery as a completely noninvasive and much more feasible approach (Blehar et al., 2014; Hossein-Nejad et al., 2015; Mackenzie et al., 2015).

The assessment of FTc is based on the measurement of the time period between the opening and closing of aortic valve during the systole (Hossein-Nejad et al., 2015; Sturgess et al., 2010). Even though this phenomenon is purely mechanical, it is in fact regulated by the electric conduction of cardiac impulses. Electrocardiography (ECG) is one of the most routinely used diagnostic tool at the emergency department and intensive care units as well as many primary-care health centers. Even though the specific hallmark of aortic valve closing could not be determined on ECG, one may conclude that FTc can be at least roughly estimated using this widely available diagnostic modality which has been commercially available since the early years of the 20th century (Rivera-Ruiz, Cajavilca, & Varon, 2008).

1.3 | Goals of this investigation

Considering the remarkable interaction between the electrophysiology and muscular function of cardiac muscles, we aimed to investigate the probable application of ECG in the estimation of FTc and volume status in healthy volunteers. To investigate FTc changes in response to changes in volume status, we deployed a passive leg raising (PLR)

maneuver which is known to increase venous return and subsequently cardiac preload by 450–500 cc (Preau et al., 2010).

2 | MATERIALS AND METHODS

2.1 | Study design and setting

This prospective study was performed between February and March 2016 at the emergency department of Imam Hospital Complex affiliated with Tehran University of Medical Sciences, Tehran, Iran. The Ethics Committee of Hospital and the Ethics Committee of Tehran University of Medical Sciences approved this study after reviewing its protocol. The aim of this study and the nature of its measurements were explained in details to all subjects before obtaining signed informed consents.

2.2 | Participants

Study subjects were healthy volunteers aged 18 or more randomly selected from the hospital employee list. Exclusion criteria were as follows: (i) refusal of participation; (ii) signs and symptoms of dehydration; (iii) a positive past medical history of cardiovascular, renal and hypertensive disorders, diabetes mellitus; (iv) mechanical abnormalities of the hearth such as valvular disease, and defects in its electrical system; and (v) cardiovascular events, blood infusion, and positive drug history of vasopressor agents in the past 3 months.

2.3 | Outcomes and data collection

The primary outcome of the study was changes in the FTc as estimated by ECG before and after PLR maneuver. Secondary outcomes of the study were changes in FTc as measured by the assessment of carotid artery via bedside ultrasonography as well as changes in HR and mean arterial pressure (MAP) before and after leg raising maneuver.

Before undergoing ECG and ultrasonography, a detailed past medical history with emphasizes on drug history followed by a brief physical examination was performed in all cases. Subjects were asked to remain in a comfortable position according to their own preferences for several minutes before undergoing study measurements. Before PLR, all exams were performed with patients' back leaned to the bed with an angle of 45° and their legs positioned parallel to each other and to the bed at the horizontal plane. PLR was then performed by positioning subjects' backs at the horizontal plane and their legs raised and leaned to the lower part of the bed with an angle of 45° for 60 s as previously described in the literature (Preau et al., 2010; Vartun, Flo, & Acharya, 2014). All measurements were repeated after PLR. All tests were performed with regard to subjects' most comfortable state in their own workplace. The attending physician and the nurse who performed ultrasonography and ECG did not wear white coat or any other type of uniforms to decrease the chance of white coat syndrome. A female nurse was deployed as a chaperone during all examinations performed on female volunteers to make the study setting as comfortable as possible.

2.4 | Ultrasonography modality

FTc was measured in real-time before and after PLR by the same attending physician of emergency medicine who performs bedside ultrasonography at a daily basis. All images were also saved on the memory of the ultrasonography device and then converted and transferred to a personal computer to be evaluated via electronic calipers in blind fashion both by the above-mentioned physician and another attending physician of emergency medicine. These findings were used to calculate intra- and interobserver reliability of this diagnostic modality. The results of Interclass Correlation Coefficient test showed Cronbach's alpha of 0.99 both for intra- and interobserver reliabilities.

The ultrasound device deployed in this study was a portable model (SonoSite Edge, SonoSite, Inc., Bothell, Washington, USA) paired with a linear array ultrasound transducer, model HFL50X, which has a frequency range 6–15 MHz. We performed digital recordings on long-axis B-mode imaging of the right common arteries by spectral Doppler waveform tracing with angle correction. FTc was measured in all cases with ease and there was no technical difficulties due to potential underlying problems such as calcification of carotid artery which would have affected the measurements. Ultrasound assessment of FTc was performed as previously described in the literature (Blehar et al., 2014; Hossein-Nejad et al., 2015), by examining the right common carotid artery adjacent the thyroid cartilage's lower border and considering an angle of insonation from 60° to 70° as acceptable. FTc was calculated by the following formula: $FTc = \text{flow time} / \sqrt{\text{cycle time}}$ (Blehar et al., 2014; Wodey et al., 2000). Figure 1 demonstrates the measurement of FTc in the carotid artery.

2.5 | Electrocardiography

ECG was performed with the standard three-lead method in all cases by an experienced nurse who performs this diagnostic modality at a daily basis at the emergency department. Prior to the conduction of the study, the performance of this nurse was evaluated by two attending physicians of emergency medicine. All examinations was done by the same device (SonoSite Edge), equipped with standard ECG leads. All ECG results in this study were measured by the above-mentioned device. As not all mechanical events of cardiac cycle could be precisely determined by ECG, we have deployed some modification in landmarks used for the calculation of FTc after reviewing the results of the pilot study on 16 cases. Flow time is defined as the time interval between the opening and the closing of aortic valve. Even though the opening of aortic valve could be determined by the end of QRS complex, the actual mechanical event of aortic valve closing falls somewhere before the end of T wave. We made a rough speculation to consider the time interval between the closing of aortic valve and the opening of AV valve as a constant ratio for all systoles with a trivial value. On the other hand, the opening of AV valve could be determined by the end of the T wave. Hence, as in the standard method, we considered the opening of aortic valve as the start point for flow time. But contrary to the standard method in which the closing of aortic valve, which has no specific landmark on ECG, is considered as the end point of flow time, we considered AV valve opening on

FIGURE 1 The measurement of flow time corrected in the carotid artery of a healthy volunteer by ultrasonography and electrocardiography

ECG as the end point for flow time. FTc was then calculated using the standard formula ($FTc = \text{flow time} / \sqrt{\text{cycle time}}$). Figure 2 provides a schematic of the mechanical and electrical features of cardiac cycle and the measurement of systolic flow time. All ECG measures were extracted by reviewing the digital output of the ECG device.

2.6 | Statistical analysis

Based on the results of the pilot study on 16 cases, a standard deviation (SD) of 25 ms was considered for both FTc as assessed via ECG or ultrasonography. Considering an alpha of 0.05, a power of 0.9, a minimum sample size of 49 cases was determined in order to detect differences of at least 10 ms in FTc measurements.

Data analysis was performed using Statistical Package for the Social Sciences (SPSS) for Windows, Version 17.0. (SPSS Inc., Chicago, IL, USA). To determine the normality of distribution of quantitative variables, normal Q-Q plots and Shapiro–Wilk test of normality were deployed. Paired t-test was deployed to evaluate the statistical significance of differences between quantitative variables including FTc measured by ultrasonography or ECG, HR, and MAP. Pearson product–moment correlation coefficient test was deployed to evaluate the relationship between FTc measure via ultrasonography with FTc estimated via ECG. Quantitative and categorical variables are presented as mean $\pm$ SD and number (percentage, %), respectively. Moreover, 95% confidence interval (95% CI) is also presented wherever indicated. *p*-Values lower than .05 were determined as the level of statistical significance of observed differences.

3 | RESULTS

3.1 | Participants' characteristics

Of 100 healthy volunteers, 2 male patients, one due to right bundle branch block and another one due to a congenital valve problem were excluded. At last, a total number of 98 subjects including

FIGURE 2 Systolic flow time as estimated via ultrasonography (FT Sono) and electrocardiogram (FT ECG). Flow time corrected (FTc) is calculated as: $FTc = \text{flow time} / \sqrt{\text{cycle time}}$

51 female subjects (52%) and 47 male subjects (48%) with a mean age of 30.69 ± 6.28 (95% CI: 29.49–32.01) years and a mean BMI of 24.74 ± 3.86 (95% CI: 23.97–25.52) were enrolled in the study. There was no report of a positive drug history for agents with potential cardiovascular or renal effects.

3.2 | Flow time corrected

Before PLR, the mean FTc was 315.29 ± 20.54 (95% CI: 311.11–319.62) $\text{ms}^{0.5}$ and 315.94 ± 18.01 (95% CI: 312.44–319.58) $\text{ms}^{0.5}$ in ultrasonography and ECG, respectively. There was no statistically significant difference between these two measures before PLR ($p = .509$). There was a significant correlation between FTc measured by ultrasonography and estimated by ECG before PLR (Pearson Correlation = 0.878, 95% CI: 0.815–0.922, $p < .0001$). After PLR, FTc increased to 337.62 ± 20.57 (95% CI: 333.39–341.79) $\text{ms}^{0.5}$ and 331.81 ± 17.64 (95% CI: 328.22–335.38) $\text{ms}^{0.5}$ in ultrasonography and ECG, respectively, which was significantly higher than pre-PLR measures ($p = .001$ for both). FTc measured via ultrasonography was higher than FTc estimated via ECG ($p = .001$). There was still a significant correlation between FTc measured by ultrasonography and estimated by ECG after PLR (Pearson Correlation = 0.797, 95% CI: 0.697–0.866, $p < .0001$). Changes in FTc was higher in measurements by ultrasonography compared to estimations by ECG (22.33 ± 17.15 [95% CI: 18.75–25.98] $\text{ms}^{0.5}$ vs. 15.86 ± 14.25 [95% CI: 11.62–16.59] $\text{ms}^{0.5}$, $p = .001$). There was also a significant correlation between changes in FTc from before to after PLR measured by ultrasonography and estimated by ECG (Pearson Correlation = 0.653, 95% CI: 0.486–0.779, $p < .0001$). Figure 3 demonstrates the correlation between FTc measured via ultrasonography and FTc estimated via ECG.

3.3 | Heart rate and mean arterial pressure

The mean HR before PLR was 78.01 ± 10.29 (95% CI: 76.08–80.21) beats per minute (bpm) which decreased to 76.63 ± 11.50 (95% CI: 74.43–78.98) bpm after PLR. The mean MAP before PLR was 83.84 ± 10.63 (95% CI: 81.57–85.94) mm Hg which increased to 85.26 ± 11.23 (95% CI: 82.99–87.40) mm Hg after PLR. The decrease in HR and the decrease in MAP following PLR were both statistically significant ($p < .0001$ for both tests). Table 1 compares study measures before and after PLR.

3.4 | Relative changes in flow time corrected, heart rate, and mean arterial pressure

The percentages of changes in FTc of carotid artery, FTc estimated by ECG, HR, and MAP from before PLR to after PLR were $7.26\% \pm 5.69\%$ (95% CI: 6.16% to 8.40%), $6.81\% \pm 4.67\%$ (95% CI: 5.93% to 8.15%), $1.70\% \pm 8.29\%$ (95% CI: 0.01% to 3.28%), and $2.13\% \pm 10.36\%$ (0.07% to 4.18%), respectively.

We further compared the amplitude of changes in FTc estimated by ECG to FTc of carotid artery estimated by ultrasonography, HR, and MAP. The magnitude of changes in FTc estimated by ECG was higher than changes in HR and MAP ($p = .002$ and $.010$, respectively), but lower than changes in FTc of carotid artery estimated by ultrasonography ($p < .0001$).

4 | DISCUSSION

The main finding of this study was the observation of a significant increase in FTc estimated by ECG following PLR. Furthermore, there

FIGURE 3 Correlation between flow time corrected (FTc, $\text{ms}^{0.5}$) of carotid artery measured via ultrasonography (Sono) and FTc estimated via electrocardiography (ECG) before passive leg raising (PLR) (a), after PLR (b), and changes from before to after PLR (c)

was a strong positive correlation between the values of FTc estimated by ECG with the values of FTc of carotid artery measured via ultrasonography. Interestingly, FTc estimated by ECG was by far more sensitive to changes in volume status compared to HR and MAP, and even though it was less sensitive to PLR compared to FTc of carotid artery, their difference was less than 10 ms and less than 0.5% of the total values of these measures which is both below the precision level of the measurements and also very unlikely to be significant at the clinical settings.

The rationale behind this study was the equal duration of electrical and mechanical functions of cardiac cycles. The assessment of FTc via Doppler ultrasonography is based on the time interval between the systolic upstroke and the dichrotic notch with correction for cycle time. These two time points are in fact created by aortic valve opening and closing, respectively. Not surprisingly, the measurement of FTc in descending aorta has been extensively described in the literature (Valtier et al., 1998). Descending aorta is the nearest artery to the heart that is accessible for study by Doppler ultrasonography and is most likely to represent the mechanical function of the heart. Despite the general acceptance of this modality for the evaluation of volume status and responsiveness in the literature, its application in the clinical settings is limited by several factors. The main shortcoming of this modality is that it could be performed almost exclusively in intubated or highly sedated patients. Moreover, the sonographer is required to blindly insert a nonimaging Doppler probe into esophagus making this modality highly operator dependable (Stawicki, Braslow, & Gracias, 2007). Maladjustment of the depth and the rotation of probe could significantly impair the accuracy of the measurement of FTc (Marik, 2013).

As a result of these limitations, there has been a growing interest in developing less invasive and more feasible modalities to estimate FTc. In one study, Blehar et al. (2014) suggested the measurement of FTc in the carotid artery, as an alternative to descending aorta, to evaluate the response to fluid therapy in dehydrated patients. Their findings indicated a significant increase of about 14% in FTc of carotid artery after patients received fluid therapy with a mean volume of 1100 ml. In another recent study, we have shown a mean reduction of 11.5% in the FTc of carotid artery after the study population underwent hemodialysis with a mean of 2400 ml of fluid removed from their intravascular compartments (Hosseini-Nejad et al., 2015). In this study, following a PLR maneuver which should increase venous return and subsequently preload by 450–500 ml (Preau et al., 2010), we have observed a mean increase of about 7% in FTc measured by either of carotid artery ultrasonography or ECG.

Some previous studies have investigated the application of diagnostic modalities based on ECG in the assessment of volume status

TABLE 1 Comparison of pre- and post-PLR Flow Time corrected (FTc, ms^{0.5}) of carotid artery measured via ultrasonography (Sono), FTc estimated via electrocardiography (ECG), heart rate (HR, beats per minute), and mean arterial pressure (MAP, mm Hg). Data are presented as mean $\pm$ standard deviation (95% confidence interval)

	Pre-PLR	Post-PLR	p-Value
FTc (Sono)	315.29 $\pm$ 20.54 (95% CI: 311.11–319.62)	337.62 $\pm$ 20.57 (95% CI: 333.39–341.79)	<.0001
FTc (ECG)	315.94 $\pm$ 18.01 (95% CI: 312.44–319.58)	331.81 $\pm$ 17.64 (95% CI: 328.22–335.38)	<.0001
HR	78.01 $\pm$ 10.29 (95% CI: 76.08–80.21)	76.63 $\pm$ 11.50 (95% CI: 74.43–78.98)	.030
MAP	83.84 $\pm$ 10.63 (95% CI: 81.57–85.94)	85.26 $\pm$ 11.23 (95% CI: 82.99–87.40)	.108

(Fresiello et al., 2015; Giraud et al., 2013; Madias & Guglin, 2007). Most of these studies have focused on Brody effect which is based on the morphologic changes in ECG as a result of changes in volume status. According to Brody (Brody, 1956), an increase in left ventricular end diastolic volume results in an increase in the amplitude to QRS voltage as blood has good electrical conductivity. In one study, Giraud et al. (2013) investigated the diagnostic applicability of Brody effect by measuring respiratory variations of QRS-wave amplitude in a pig model of hemorrhagic shock. They showed that changes in QRS amplitude is strongly correlated both with a decrease and increase of 40% of the total blood volume. While the applicability of such modalities at the clinical setting is yet to be established, assessment of FTc has been extensively evaluated by many studies (Lee et al., 2007; Mackenzie et al., 2015; Sturgess et al., 2010; Su et al., 2014; Yang et al., 2013) and its main limitation is the feasibility of the procedure which is not an issue with ECG recording modality via ultrasound device. It should also be noted that PLR maneuver has much less effects on cardiac status in healthy subjects as opposed to acute hemorrhage or dehydration in critically ill patients. Hence, it is likely that the sensitivity of both measures of FTc by ultrasonography and ECG is higher than estimations achieved from our results. For comparison with the above-mentioned study on a pig model, a decrease of 40% in total human blood would equal to about 2000 cc, resulting in hypovolemic shock of grade III or IV, a life-threatening condition (Guly et al., 2010).

There seems to be a strong correlation between FTc of carotid artery measured via Doppler ultrasonography and FTc estimated from ECG. As the observed difference in the values of FTc resulted from these two modalities seems to be trivial, it can be recommended to further investigate the use of ECG in the assessment of volume status. Compared to other noninvasive modalities, ECG is routinely practiced by nursing staff, is much easier to master, is much less operator dependent, and does not require expertise in contrast to ultrasonography.

This study provides a valid evaluation of the possible application of FTc estimated by ECG to assess intravascular volume status. However, several limitations should be considered to not overgeneralize its findings. First, due to the lack of a feasible gold standard modality for the evaluation of volume status, we compared our findings with FTc of carotid artery measured by ultrasonography, HR, and MAP. Second, the study population was healthy volunteers of Caucasian race and their findings may be slightly different to people of other races such as Asians, Blacks, Hispanics, and even those of different ethnicities within Caucasian race. Third, as both preload and the inotropic characteristics

of the heart could affect FTc (Singer et al., 1991; Wodey et al., 2000), its values may be altered in patients with underlying renal or cardiovascular problems or recipients of blood pressure regulating agents. Further studies are warranted to determine the independent effects of each of such factors on the measurement of FTc. Forth, the device we used to digitally determine the landmarks of cardiac cycle via ECG had a precision of 10 ms. Moreover, in some cases, the endpoint of QRS complex may not be precisely evaluated due to the shape of the wave. Finally, it is well known that compared to dehydrated patients, well-hydrated individuals are less prone to significant changes in volume status indices following receiving fluids or increase in their venous return as their compensatory mechanisms could response rapidly to mild-to-moderate changes. Hence, the magnitude of changes are likely to be greater in acutely dehydrated patients compared to our study population.

In conclusion, the findings of this study suggest a potential role for the use of ECG in the assessment of volume status as a noninvasive, widely available, easy to use, and time-saving modality. Further research should emphasize on the applicability of this approach at different clinical settings and standardization of the interpretation of its findings.

CONFLICT OF INTEREST

The authors have no conflict of interest and nothing to disclose.

AUTHOR CONTRIBUTIONS STATEMENT

HH designed the study and supervised its process. PM provided advice on the study design and wrote the draft. AZ provided statistical advice and performed the data analysis. SS managed the recruitment of subjects and supervised the study process. MB performed the measurements and takes responsibility for the article as a whole. All authors reviewed the manuscript and contributed significantly to its revision.

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